B.C. Centre for Excellence in HIV/AIDS Pharmacovigilance Initiative

Annual Report: 2023

BRITISH COLUMBIA CENTRE *for* EXCELLENCE *in* HIV/AIDS

Providence Health Care St. Paul's Hospital

BRITISH COLUMBIA Ministry of Health

Disclaimer:
The BC Centre for Excellence in HIV/AIDS (BC-CfE) Pharmacovigilance Initiative receives reports of suspected adverse drug reactions, drug interactions and other adverse drug-related events associated with the use of antiretroviral medications for HIV treatment and pre-exposure prophylaxis. The information provided in this report summarizes post-marketing experience with antiretroviral therapy in persons who receive HIV medications through the BC-CfE Drug Treatment Program or Pre-Exposure Prophylaxis (PrEP) program. Reports of adverse drug-related events are voluntarily submitted by health care providers, patients and care-givers and are not systematically evaluated for accuracy or for the strength of evidence regarding the causal relationship between drug exposure and observed effect.

Information from reports of adverse drug-related events is stored in the BC-CfE Registry, a secure, computerized database. This database is updated on a regular basis. Figures and tables provided in the Annual Report represent the best estimates available at the time this document was published.

Figures and graphs presented in this document are best viewed in colour.

Statement of Confidentiality:
The personal information of patients and their health care providers is private and confidential. De-identified data are used for the purpose of drug safety surveillance in accordance with British Columbia Privacy legislation.

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Introduction

The BC-CfE Pharmacovigilance Initiative collects, evaluates, and analyzes reports of drug toxicity and other adverse drug-related events associated with antiretroviral medications, and uses this information to understand and prevent drug-related problems.

Adverse drug reactions ("side-effects") to antiretroviral medications and interactions between antiretroviral medications and other drugs can affect patients' health and interfere with treatment success. All drugs are tested for safety before they are approved for sale in Canada; however, pre-marketing clinical trials cannot study enough patients to be able to detect adverse drug-related events that are rare, take a long time to develop, or occur more frequently in people with certain risk factors. These toxicities may be discovered after a drug is used in the general population

Ongoing monitoring of adverse drug-related events is required to detect unexpected toxicities as soon as possible, so that health care providers and patients can be warned of new safety concerns.

Acknowledgement

The Pharmacovigilance Initiative acknowledges with thanks the support provided by clerical staff, data analysts and programmers at the BC Centre for Excellence in HIV/AIDS, the staff of the St Paul's Hospital Ambulatory Pharmacy, and all those who report adverse drug-related events and Drug Treatment Program and PrEP program participants.

Conflict of Interest Declaration

The BC-CfE Pharmacovigilance Initiative does not receive pharmaceutical industry funding. The authors of this report have no conflicts of interest to declare within the past 3 years**.**

Definitions and abbreviations

The following definitions and abbreviations apply to terms used throughout this document. Terms that relate to a particular section of the report are defined within that section.

- **BC-CfE:** BC Centre for Excellence in HIV/AIDS

- **Adverse drug-related event:** Any untoward event associated with a medication. The BC-CfE captures events including (but not limited to) the following event categories*:*
    - **Adverse drug reaction (ADR):** A suspected adverse drug reaction (unintended, undesirable effect of an antiretroviral medication) attributed to one or more antiretroviral drugs. Includes events in which the medication is continued, dose adjusted or discontinued.
    - **ADR prevention:** Antiretroviral therapy is changed to prevent a potential adverse drug reaction.
    - **Drug interaction, symptomatic:** An adverse drug reaction resulting from a drug interaction between an antiretroviral medication and another drug.
    - **Drug interaction prevention:** Antiretroviral medication is discontinued or the dose is adjusted to prevent a potentially harmful drug interaction with another medication (no ADR occurred).

- **Adverse drug-related event information source:**
    - **Prescription:** All requests for new antiretroviral regimens for HIV treatment or pre-exposure prophylaxis must be reviewed and approved by the BC-CfE Drug Treatment Program. The 'Prescription Request' form includes a section for reporting adverse drug-related events.
    - Prescribers may also document adverse drug-related events on refill prescriptions for ongoing regimens.
    - **Therapy interruption alert/ Late refill notification:** BC-CfE mails Therapy Interruption Alerts to prescribers if the patient's refill history suggests a >2-month gap in therapy for HIV treatment or >3-month gap for PrEP. Forms include a section for reporting adverse drug-related events.
    - **Spontaneous report:** A report voluntarily submitted directly to the BC-CfE Pharmacovigilance Initiative.

- **ARV, antiretroviral drug:** Medications used to treat or prophylax against Human Immunodeficiency Virus (HIV) infection.
- **ART, antiretroviral therapy:** Combination of ARVs comprising the treatment regimen.
- **HIV-tx, HIV treatment:** Use of combination ART for the treatment of HIV infection (in HIV-positive persons).
- **PrEP, pre-exposure prophylaxis:** Use of certain ARVs to reduce the risk of acquiring new HIV infection.
- **Antiretroviral drug classes:**
    - NRTI: Nucleoside (-tide) reverse transcriptase inhibitor
    - NNRTI: Non-nucleoside reverse transcriptase inhibitor
    - PI: Protease inhibitor
    - INSTI: Integrase strand transfer inhibitor
    - PK enhancer: Pharmacokinetic enhancer ("booster")

Reports of adverse drug-related events associated with antiretroviral medications

Tables 1a-b and 2a-b summarize all reports of adverse drug-related events associated with antiretroviral use for HIV treatment and pre-exposure prophylaxis (PrEP), respectively. Overall reporting of events related to HIV treatment continued to decline in 2023, following a transient spike in preventative ART regimen changes in 2020 (See also: Figure 11). Reports of adverse drug-related events related to PrEP medication remained stable in 2023.

Table 1a. Adverse drug-related events associated with ART for HIV treatment – Five-year summary

Year	Number of patients receiving antiretroviral treatment	Adverse Drug-Related Event reports All categories, excluding duplicates	
		Total per year	Average per month
2019	8100	918	77
2020	8111	1045	87
2021	8150	742	62
2022	8225	531	44
2023	**8324**	**460**	**38**

Table 1b. Adverse drug-related events associated with ART for HIV treatment- 2023

Information Category	Reports including duplicates N=532 n (%)	Reports excluding duplicates N=531 n (%)
Event Type		
Adverse Drug Reaction	294 (64)	292(63)
Adverse Drug Reaction Prevention	80 (17)	80 (17)
Drug Interaction Prevention	83 (18)	83 (18)
Drug Interaction, Symptomatic	5 (1)	5 (1)
Information Source		
Prescription	457 (99)	*
Therapy Interruption Alert	1 (<1)	*
Spontaneous Report	4 (1)	*
Reporter Type		
Physician	337 (73)	*
Pharmacist	125 (27)	*
Other Healthcare professional	0 (0)	*
Patient/ Consumer	0 (0)	*

*Not applicable; multiple reporter or information source categories are possible for each event

Table 2a. Adverse drug-related events associated with ARVs for PrEP– Five-year summary

Year	Number of patients receiving PrEP	Adverse Drug-Related Event reports All categories, excluding duplicates	
		Total per year	Average per month
2019	5008	56	5
2020	5334	39	3
2021	5901	41	3
2022	7357	51	4
2023	**8211**	**70**	**6**

Table 2b. Adverse drug-related events associated with ARVs for PrEP- 2023

Information category	Reports including duplicates N=52 n (%)	Reports excluding duplicates N=51 n (%)
Event Type		
Adverse Drug Reaction	67 (93)	65 (93)
Adverse Drug Reaction Prevention	5 (7)	5 (7)
Drug Interaction, Symptomatic	0 (0)	0 (0)
Information Source		
Prescription	62(86)	*
Spontaneous Report	7 (10)	*
PrEP Interruption Alert	3 (4)	*
Reporter Type		
Physician	59 (82)	*
Pharmacist	2 (3)	*
Other Healthcare professional	11 (15)	*

*Not applicable; multiple reporter or information source categories are possible for each event

Adverse drug reactions (ADRs) associated with ART for HIV treatment and PrEP

As shown in **Figure 1**, there was a sharp drop-off and subsequent rebound in reporting rates of ADRs related to ART for HIV treatment in 2020 (COVID-19 pandemic-related disruptions), followed by a gradual decline in ADR rates, ongoing in 2023. ADR rates related to HIV pre-exposure prophylaxis have been relatively stable since the launch of the PrEP program in 2018.

Figure 1. Adverse drug reactions associated with ART for HIV treatment and pre-exposure prophylaxis (all drugs) – Five-year reporting patterns, by quarter

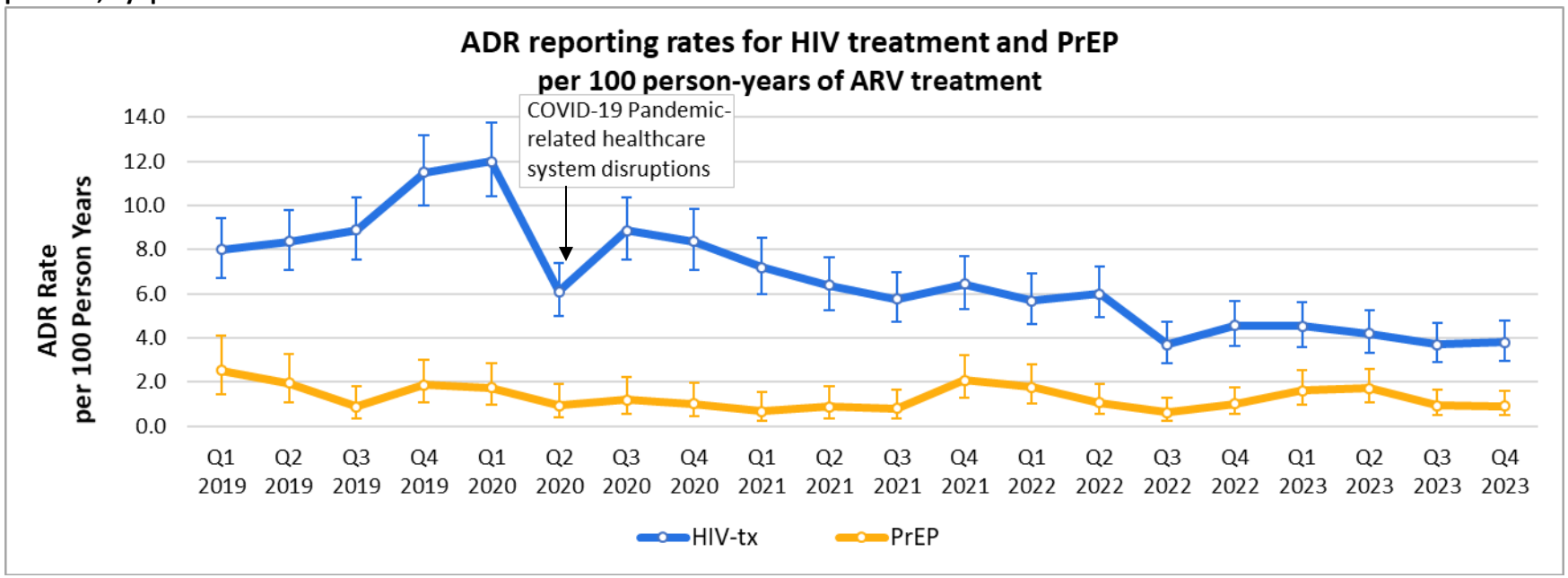


Figure 1 notes: Quarterly ADR rates in persons receiving ARVs for HIV treatment (HIV-tx) and pre-exposure prophylaxis (PrEP). Within each quarter (3-month period), the numerator is the number of ADR reports for ART-treated persons (excluding duplicates, events with unlikely causality and ART changes to prevent ADRs or drug interactions). The denominator is the total number of patient-years of ART exposure accrued during the quarter. Rates are expressed per 100 person-years of treatment. Error bars around each point display the 95% confidence interval, calculated by the Poisson method (using Byar approximation).

Adverse drug reaction (ADR) rates by antiretroviral drug class

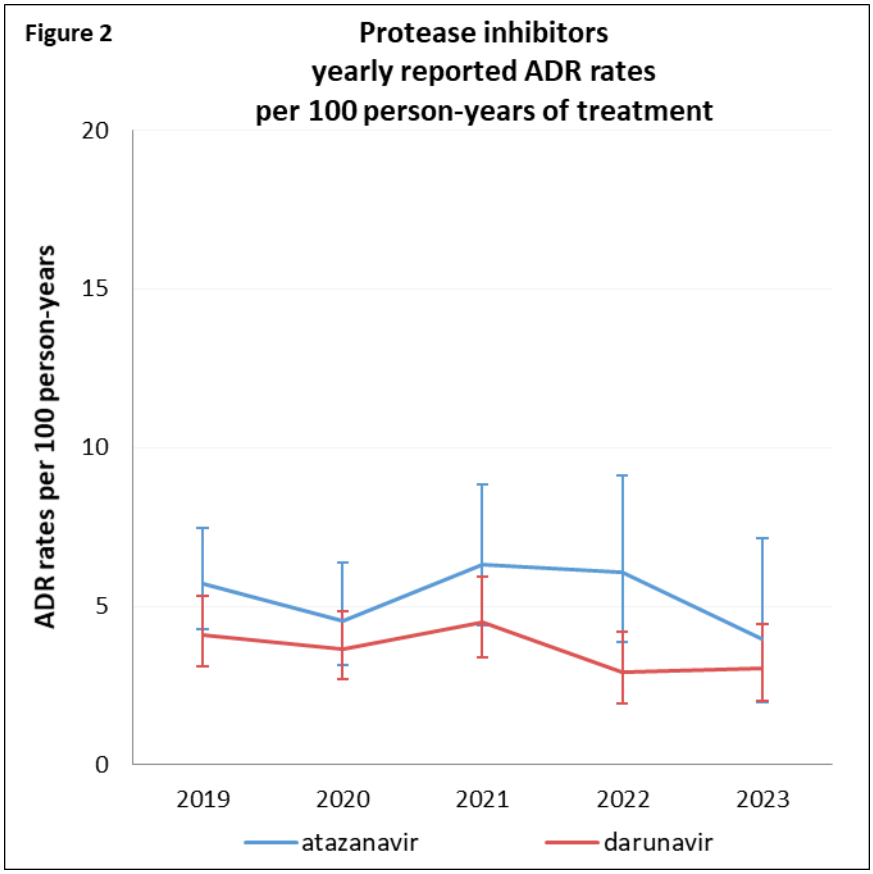
This section focuses on ART for HIV treatment. Information regarding PrEP is included in the relevant sections.

Figures 2 to 5 display annual ADR rates over the past five years for the most commonly used ARVs. For each ARV, ADR rates are shown for all persons treated during the calendar year. See Appendix for details regarding calculation of rates.

2023 reporting year highlights:

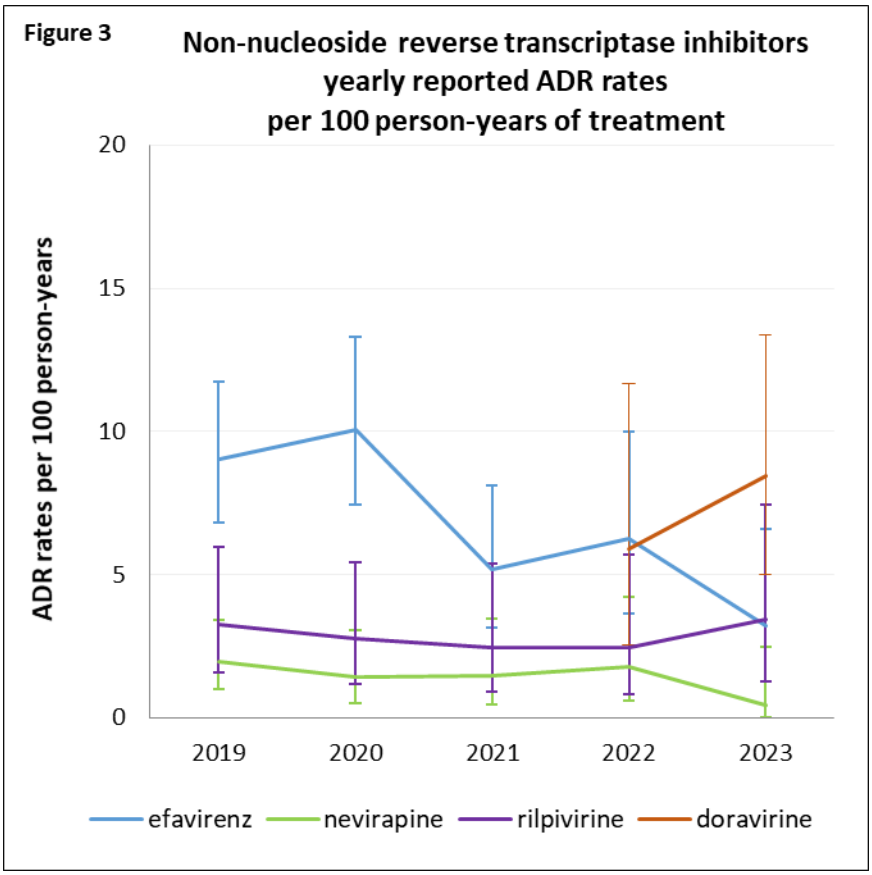
- **Figure 2:** The use of PIs is declining. Gastrointestinal adverse effects continue to be the most commonly reported ADRs for darunavir, while hepatic (isolated hyperbilirubinemia, a non-harmful increase in bilirubin levels) and renal (nephrolithiasis) were most commonly reported for atazanavir.
- **Figure 3:** The use of NNRTIs other than doravirine is declining. Neuropsychiatric and gastrointestinal effects continue to be the most commonly reported NNRTI ADRs.
- **Figure 4:** The second generation INSTIs dolutegravir and bictegravir account for the majority of INSTI usage. Neuropsychiatric effects, gastrointestinal upset and unintentional weight gain remain the most commonly reported ADRs with these newer INSTIs.
- **Figure 5:** For HIV-tx clients, the shift in prescribing patterns from tenofovir DF to tenofovir AF, and decline in abacavir use continues, with tenofovir-related renal and bone health-related toxicities continuing to be the most commonly reported ADRs. Weight gain is increasingly reported with tenofovir AF, possibly influenced by co-formulation with the INSTI bictegravir. The tenofovir ADR rate is lower for PrEP clients than HIV-tx clients

Figure 2. Protease inhibitor ADR rates associated with ART for HIV treatment



Number of adverse drug reaction (ADR) reports / Total person-years drug exposure					
	2019	**2020**	**2021**	**2022**	**2023**
atazanavir	54/ 947	34/ 747	34/ 538	23/ 378	11/276
darunavir	57/ 1390	47/ 1286	52/ 1152	29/ 997	27/884

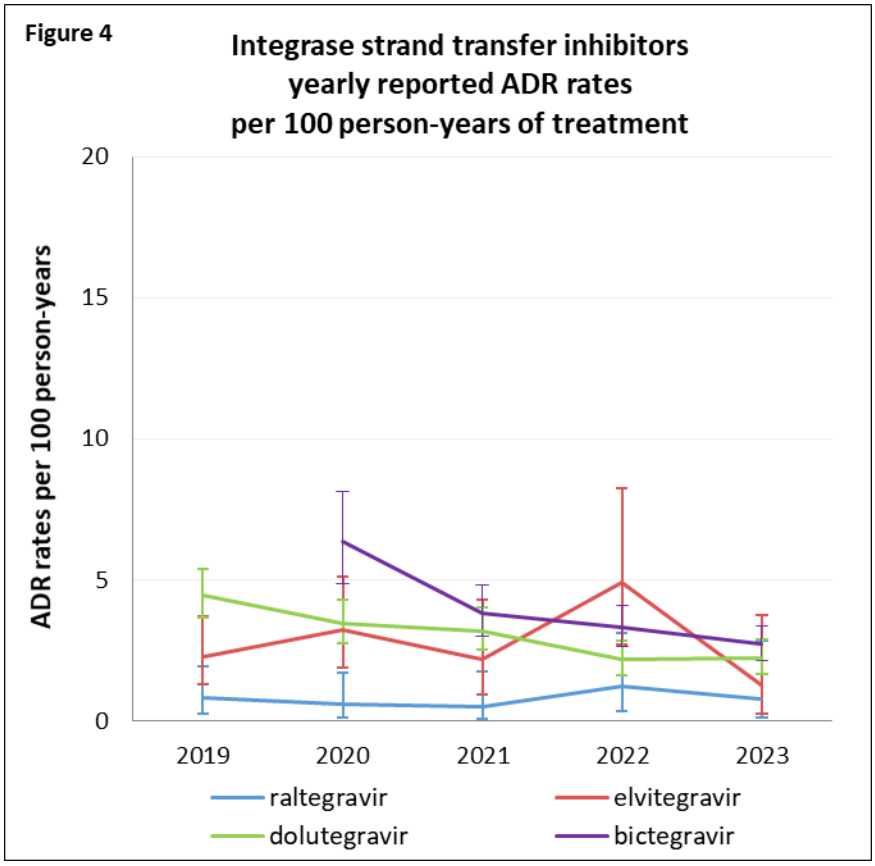
Figure 3. Non-nucleoside reverse transcriptase inhibitor ADR rates associated with ART for HIV treatment



Number of adverse drug reaction (ADR) reports / Total person-years drug exposure					
	2019	**2020**	**2021**	**2022**	**2023**
doravirine	No data	Limited data	6/ 43	8/ 135	18/213
efavirenz	55/ 610	49/ 487	19/ 366	17/ 272	7/219
etravirine	<5/ 204	<5/ 177	<5/ 145	<5/ 115	<5/91
nevirapine	12/ 617	6/ 427	5/ 337	5/ 278	<5/226
rilpivirine*	10/ 308	8/ 291	6/ 243	5/ 204	6/176

*Rilpivirine includes both oral and injectable forms.
Etravirine is not displayed in the figure due to low ADR rates.

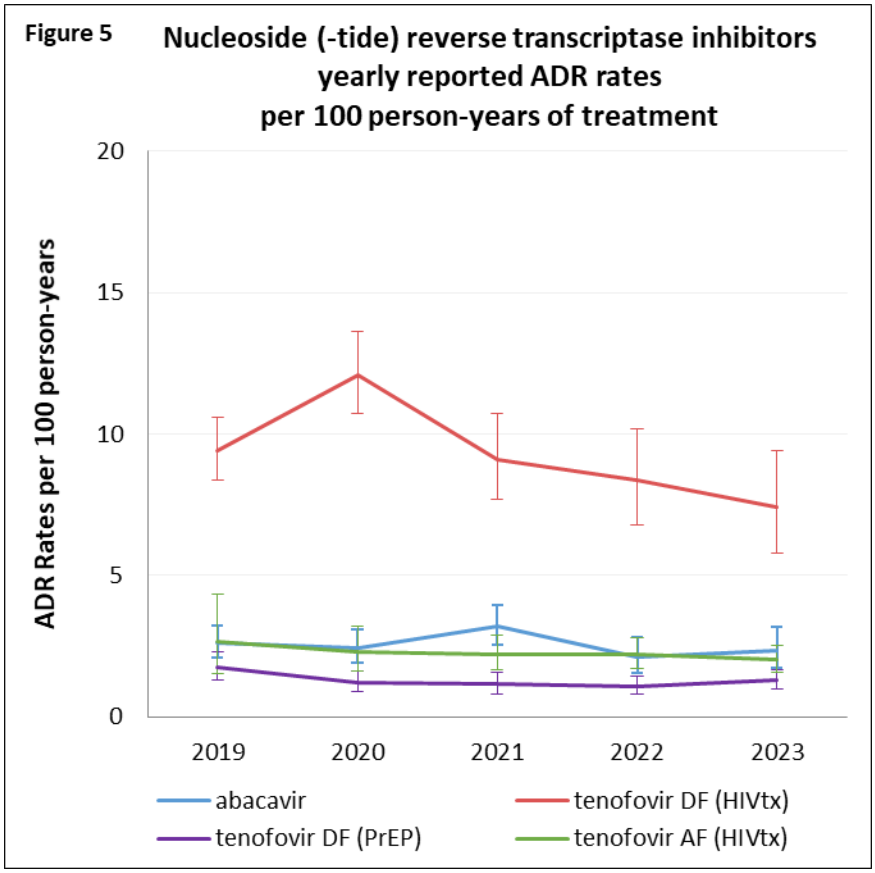
Figure 4. Integrase strand transfer inhibitor ADR rates associated with ART for HIV treatment



Number of adverse drug reaction (ADR) reports / Total person-years drug exposure					
	2019	**2020**	**2021**	**2022**	**2023**
raltegravir	5/ 608	<5/ 511	<5/ 413	<5/ 331	<5/256
elvitegravir	16/ 706	17/ 531	8/ 367	14/ 285	<5/234
dolutegravir	110/ 2464	84/ 2426	76/ 2381	51/ 2353	53/2408
bictegravir	Limited data	62/ 978	74/ 1939	85/ 2569	83/3033

Cabotegravir (oral and injectable) became available in BC in 2023. Not displayed due to limited data.

Figure 5. Nucleoside (-tide) reverse transcriptase inhibitor ADR rates associated with ART for HIV treatment and PrEP



Number of adverse drug reaction (ADR) reports / Total person-years drug exposure					
	2019	**2020**	**2021**	**2022**	**2023**
abacavir	83/ 3165	71/ 2951	82/ 2605	47/ 2196	45/1903
tenofovir DF (HIV tx)	285/ 3033	279/ 2307	146/ 1601	98/ 1172	70/940
tenofovir DF (PrEP)	52/ 3025	33/ 3194	37/ 3379	46/ 4263	63/4871
tenofovir AF (HIV tx)	16/ 597	35/ 1523	54/ 2442	67/ 3034	70/3479

Tenofovir AF, tenofovir alafenamide; Tenofovir DF, tenofovir disoproxil fumarate.
ADR rates associated with use of tenofovir DF for HIV treatment (HIV-tx) and pre-exposure prophylaxis (PrEP) are reported separately.

Adverse Drug Reaction Rates by Symptom Category, associated with ART for HIV treatment

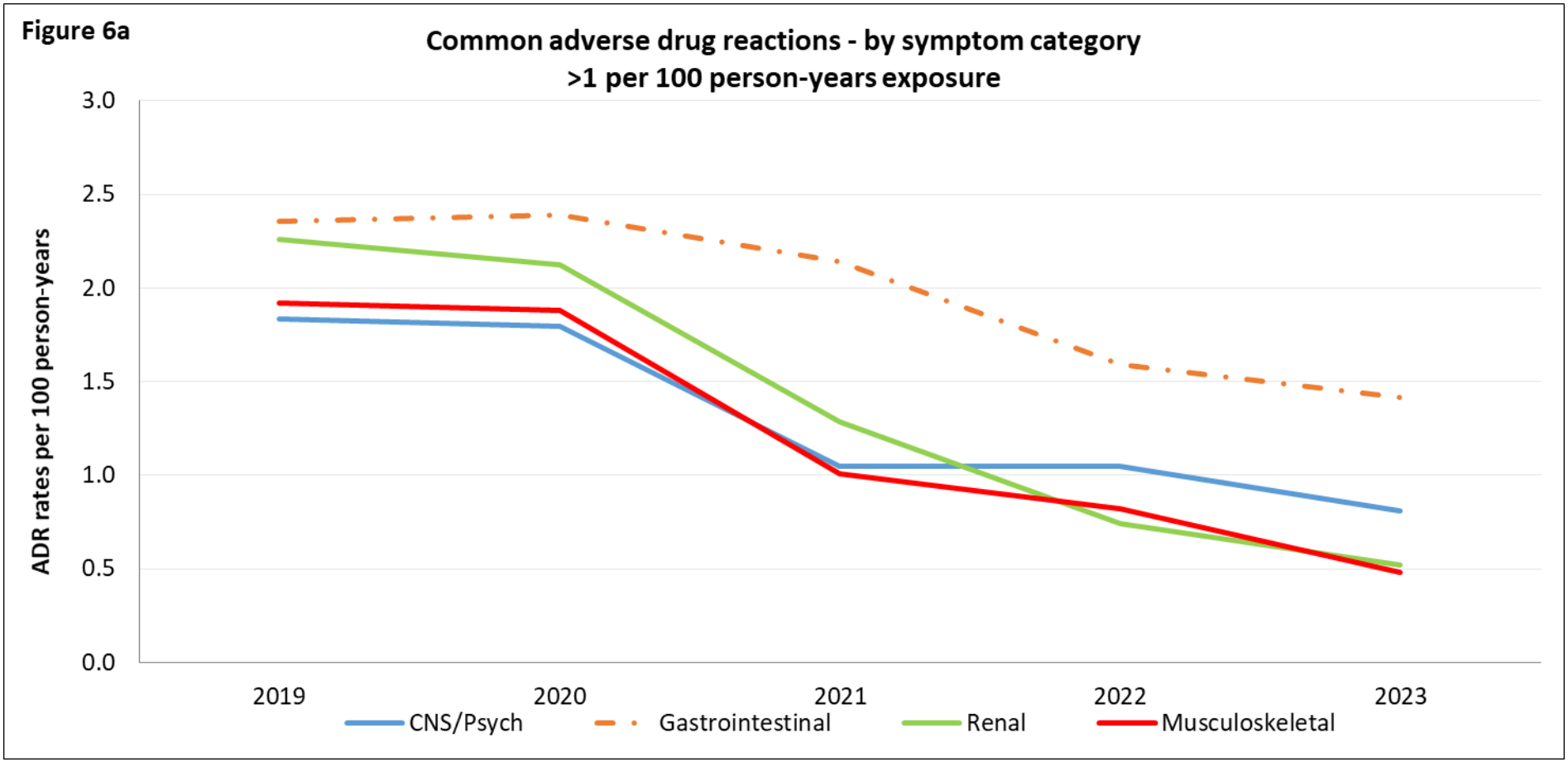
Figures 6a and 6b display annual ADR rates over the past five years by symptom category

Symptom category summaries are organized by body system. For visual clarity, symptom categories are grouped into common (>1) and uncommon (0.1 to 1) ADR events per 100 person-years of ART exposure, displayed in Figures 6 a and b, respectively, and error bars are not displayed in the graphs.

See Appendix for details regarding calculation of rates.

2023 reporting year highlights: Although gastrointestinal, central nervous system, renal and musculoskeletal (bone health) concerns continue to be the most commonly reported ARV-associated ADRs (Figure 6a), ADR rates of these symptoms are declining, consistent with the overall decline in ADR rates. “General” side effects (Figure 7b) include unintentional weight gain. Consistent with the literature, second generation INSTIs (dolutegravir, bictegravir) and the NRTI tenofovir AF are most commonly implicated in reports of unintentional weight gain.

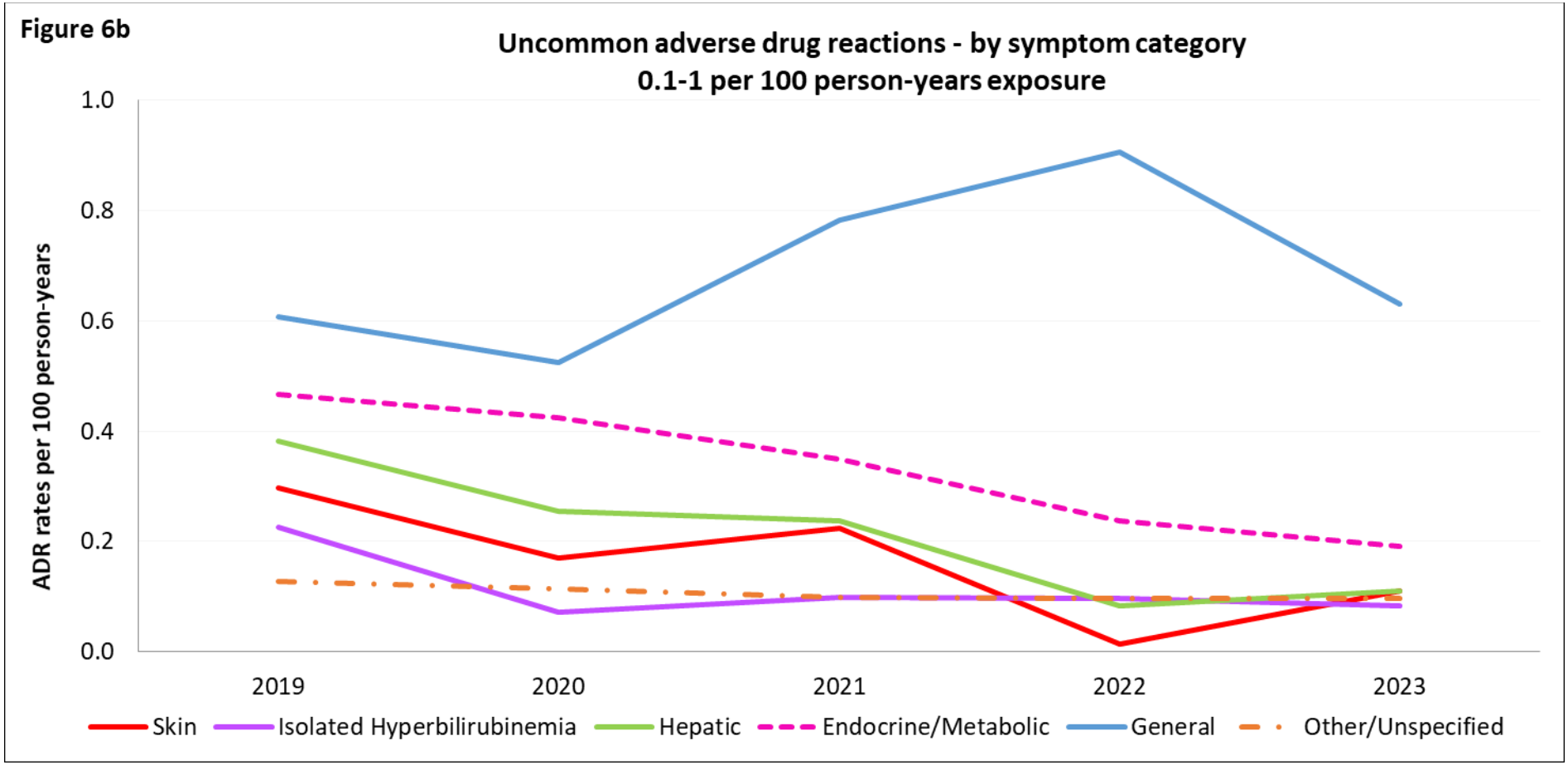
Figure 6a



Symptoms under these category headings may include the following. This is not a comprehensive list of all symptoms included:

Central nervous system/ Psychiatric (CNS/Psych):	Insomnia/ sleep disorder, nightmares/vivid dreams, headache, altered mood, altered mental status
Gastrointestinal (GI):	GI upset/ discomfort, nausea and/or vomiting, difficulty swallowing medication (“pill size”), diarrhea
Musculoskeletal:	Bone mineral loss (osteopenia, osteoporosis), myalgia/arthralgia
Renal:	Serum creatinine elevated/GFR low, proteinuria, nephrolithiasis, renal impairment (unspecified)

Figure 6b



Symptoms under these category headings may include the following. This is not a comprehensive list of all symptoms included:

Endocrine/ Metabolic:	Lipid abnormalities (e.g. elevated cholesterol), low serum phosphorus
General:	Unintentional weight gain/(loss), fatigue/malaise/low energy, general allergic reaction
Hepatic:	Hepatic transaminases (AST/ALT) elevated, cholelithiasis, abnormal liver function tests (unspecified)
Isolated Hyperbilirubinemia:	Hyperbilirubinemia ± jaundice
Skin:	Rash/hives, itching (no lesions)
Other/ Unspecified:	Other/ unspecified adverse reactions

Serious or unexpected adverse drug reactions associated with ART for HIV treatment or PrEP

In support of national and international drug safety monitoring programs, the BC-CfE Pharmacovigilance Initiative reports serious or unexpected adverse drug reactions to the Health Canada Vigilance Program, which in turn submits reports to the World Health Organization. Serious adverse drug reactions include those of grade IV severity (potentially life-threatening) and/or those resulting in hospital admission, prolongation of hospital stay or death. Unexpected reactions include clinically important events associated with newly marketed drugs, or rare adverse reactions associated with established drugs.

In 2023, there were a total of 362 adverse drug reaction reports received for HIV drug treatment and PrEP program clients combined (excluding duplicates). A total of 16/362 (4.4%) ADR reports were submitted to Health Canada. These included 13/297 (4.4%) of ADR reports for HIV treatment clients and 3/65 (4.6%) of reports received for PrEP clients. In total 3/362 (0.8%) were classified as serious ADRs.

Adverse drug reactions associated with ART for HIV treatment in special populations

Figures 7a-b and 8a-b display ADR reports stratified by age and sex, respectively. These analyses are limited to HIV treatment program participants, due to low numbers of seniors and females in the PrEP program.

Adverse drug reactions associated with ART for HIV treatment, by age category

In 2023, 17% of persons receiving ART for HIV treatment were seniors age ≥65 years. The proportion of seniors with a reported ARV ADR was similar to the proportion of younger persons with ADRs (3.7% vs. 3.5%, respectively), which was not a statistically significant difference (p = 0.711). ADRs most commonly reported in seniors were similar to the general population, with gastrointestinal, renal, musculoskeletal (bone health), and neuropsychiatric (sleep disturbances, dizziness) symptoms accounting for the majority of reports (listed in declining order of frequency).

Figure 7a. ART-treated persons in BC, by age category

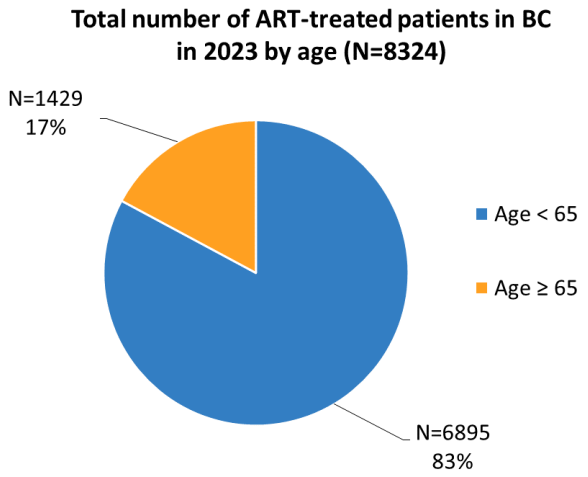
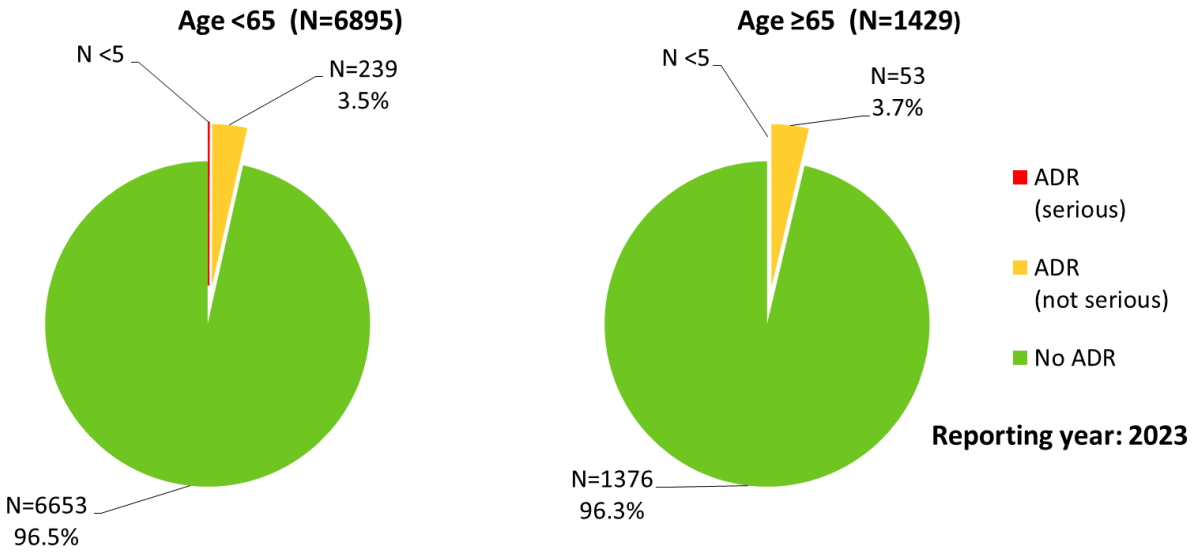


Figure 7b. Proportion of ADR reports in ART-treated persons, stratified by age category



Adverse drug reactions associated with ART for HIV treatment, by biological sex

In 2023, 17% of the total ART-treated population were persons of female biological sex. The proportion of females with a reported ARV ADR was higher than for males (5.5% and 3.1%, respectively), which was a statistically significant difference (p <0.001). ADRs most commonly reported in females were similar to the general population, with gastrointestinal, general (weight gain, fatigue), central nervous system (sleep disorder, headache), and musculoskeletal (bone health) symptoms accounting for the majority of reports (listed in declining order of frequency).

Figure 8a. ART-treated persons in BC, by biological sex

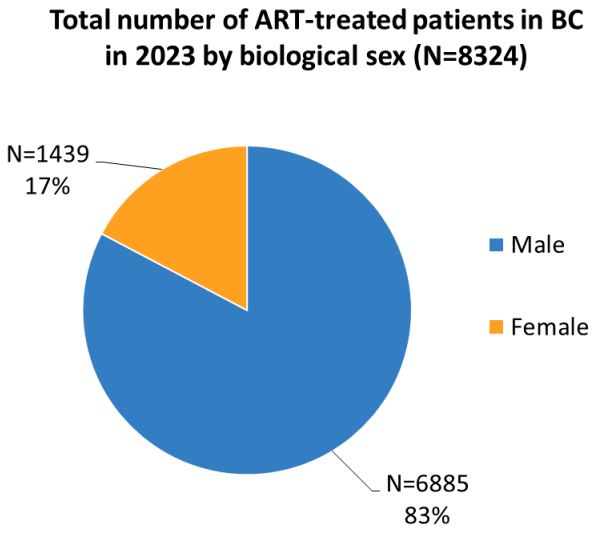
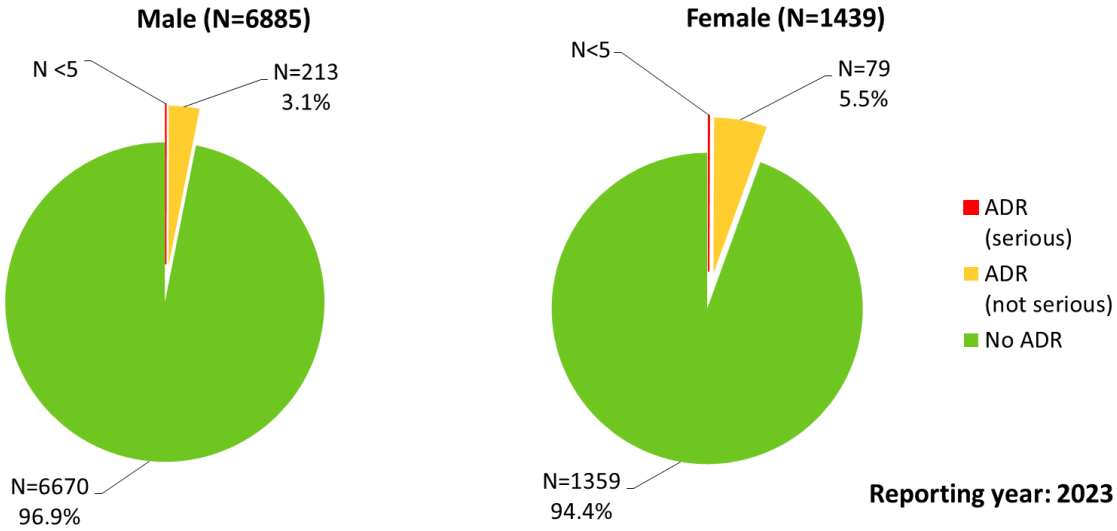


Figure 8b. Proportion of ADR reports in ART-treated persons by biological sex



Drug interactions associated with ART for HIV treatment

Figures 9 and 10 summarize antiretroviral drug interaction reporting patterns in 2023.

The pharmacokinetic enhancers (“boosters”) cobicistat and ritonavir accounted for the majority of ART therapy changes related to drug interactions between HIV medications and other drugs.

Drug interactions with corticosteroids (e.g. inhalers and intra-articular injections), cardiovascular drugs (e.g. anticoagulant and antiplatelet medications), gastrointestinal drugs (e.g. drugs that suppress gastric acid, such as proton pump inhibitors), and anti-infective drugs (e.g. for treatment of tuberculosis, hepatitis C) are among the most common interacting medications.

Figure 9. Antiretroviral drug interactions by ARV class

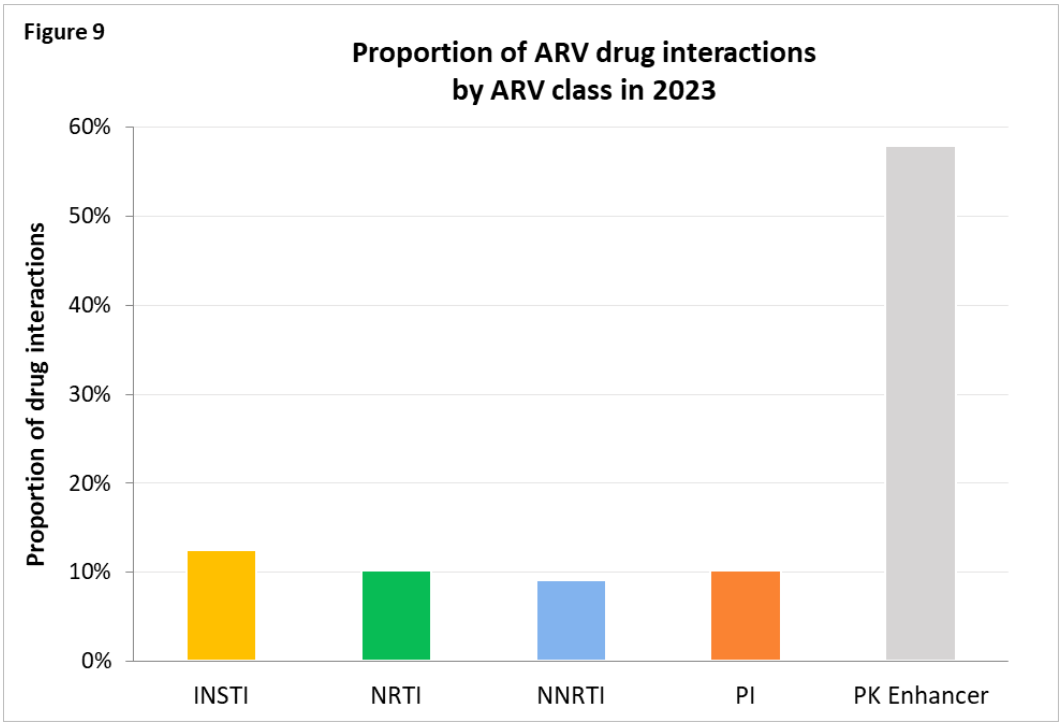
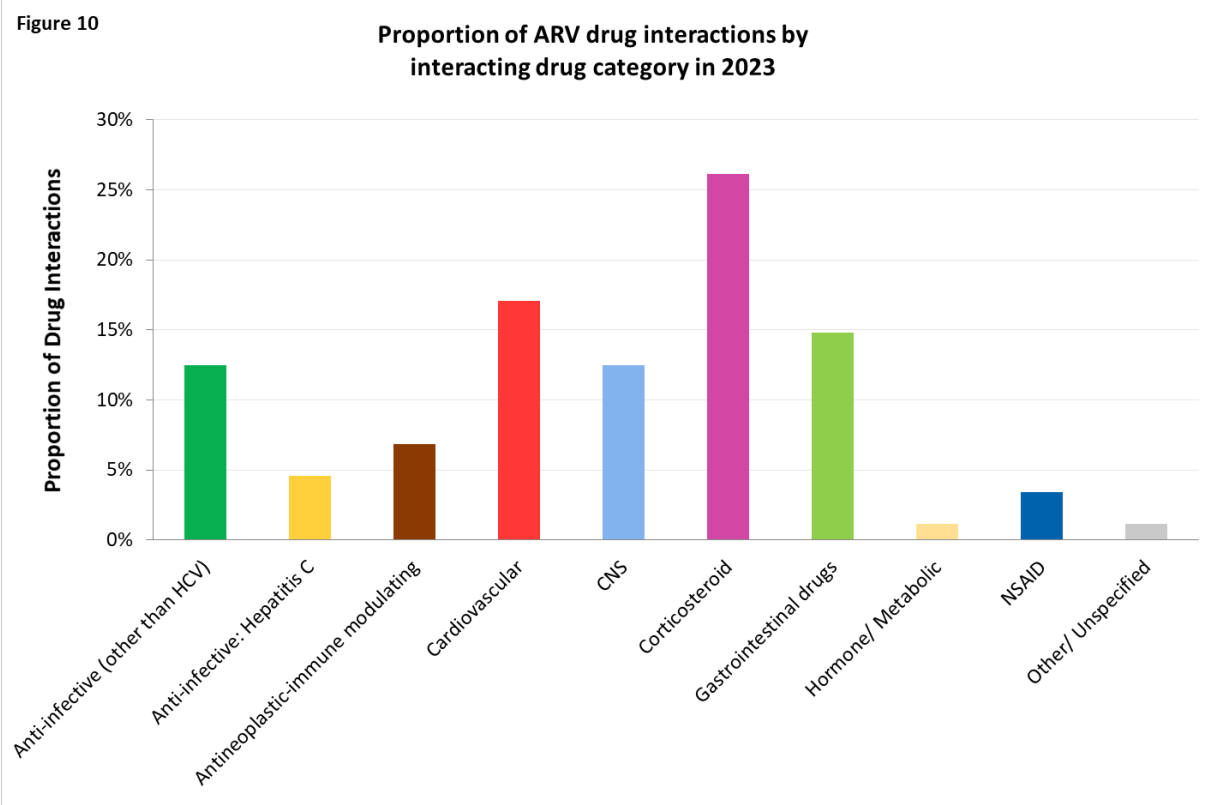


Figure 10. Antiretroviral drug interactions by interacting drug category



Figures 9 and 10 notes: PK enhancer, Pharmacokinetic enhancer ("booster") ritonavir or cobicistat; ARV-tx Patients, Drug Treatment Program participants receiving antiretrovirals for treatment of HIV; CNS, Central nervous system; NSAID, non-steroidal anti-inflammatory

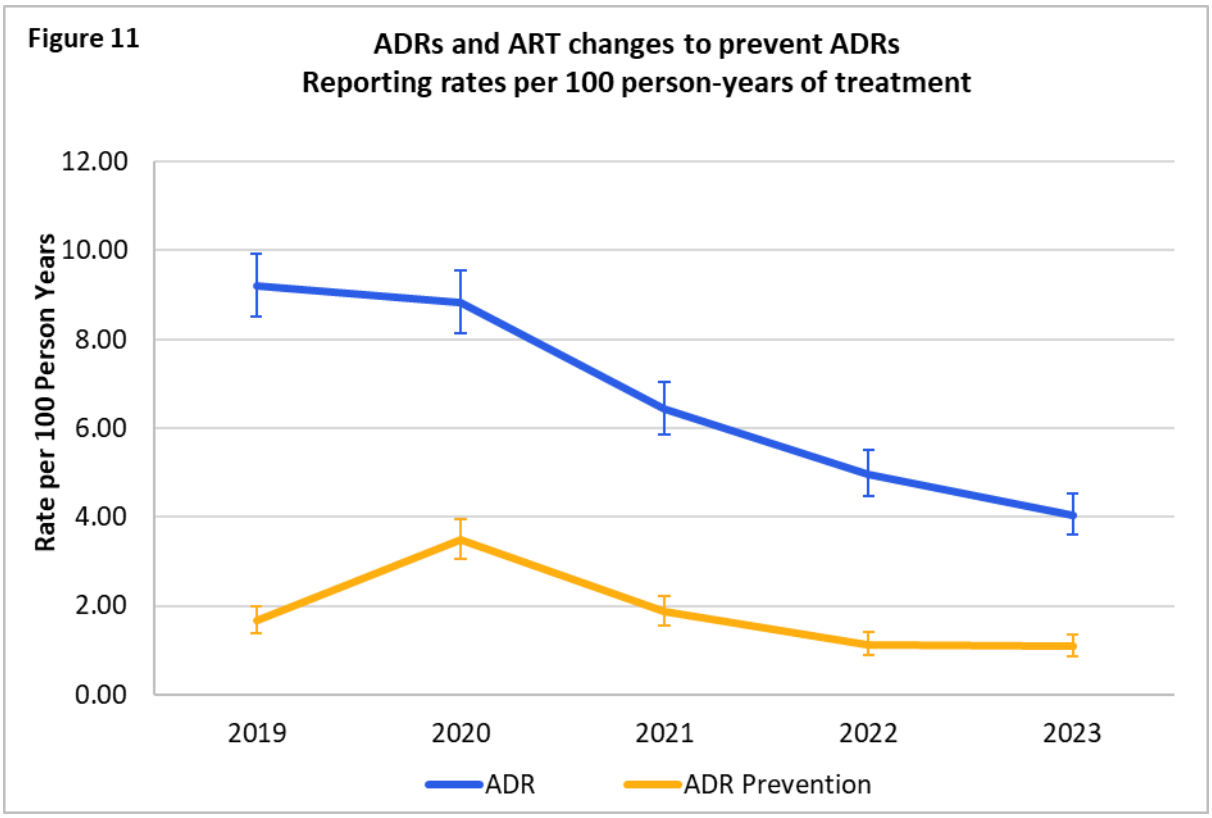
ART changes for Prevention of Adverse Drug Reactions in persons receiving HIV treatment

Antiretroviral therapy changes for the purpose of preventing a potential ADR, such as reducing the long-term risk of renal injury, are documented as "ADR prevention", and are monitored separately from symptomatic ADRs. Reports of ADR prevention are only captured when the prescriber documents this intention on a request for ARV regimen change, and therefore the actual incidence of preventative regimen changes is likely underestimated.

Figure 11 shows the pattern of ART changes for ADR prevention in relation to reports of ADRs. In 2019 and 2020 there was a spike in preventative ARV regimen changes, associated with a shift to newer ARVs. Since 2021, there has been an overall decline in all ADR reports, including "ADR prevention".

In 2023, the ARVs most commonly implicated in preventative changes are tenofovir DF (long term renal and bone health concerns), abacavir (cardiovascular risk reduction), and atazanavir (avoiding risk of renal stones).

Figure 11. Five-year reporting rates for ADRs and ART changes to prevent ADRs associated with ART for HIV treatment (all drugs)



How to report an Adverse Drug Reaction to BC-CfE Pharmacovigilance

Reports of suspected ADRs may be submitted to the BC-CfE Pharmacovigilance Initiative in several ways:

Any health care provider or person taking antiretroviral medication for HIV treatment or pre-exposure prophylaxis
(PrEP) may report an antiretroviral ADR by completing an Antiretroviral Adverse Drug Reaction Report form. Click to download ADR report form. Fax or mail the completed report to the address shown on the form.

Alternately, health care providers may choose to report suspected ADRs to the BC-CfE Pharmacovigilance Initiative in the following ways, instead of completing the ADR Report form:

Report on the HIV Drug Treatment Program or PrEP Program Prescription form:

For HIV Drug Treatment Program (DTP) clients, describe the suspected drugs and reaction in the "Reason(s) for medication change" section of the prescription request form. Click here to access DTP documents

For PrEP program clients, describe the suspected drugs and reaction on the prescription request or refill prescription form. Click here to access PrEP documents

Report on the HIV Drug Treatment Program or PrEP program therapy interruption/adherence Alert:

If a Drug Treatment Program or PrEP program client does not refill their prescribed ARV medications for more than two to three months after the expected refill date, a therapy interruption/adherence Alert is mailed to the client's health care provider to support continuity of care.
The Alerts include the opportunity for healthcare providers to provide an update regarding the client's current treatment status, including an opportunity to report ADRs.

Report by telephone:

To submit a confidential adverse drug reaction report by telephone, contact the BC-CfE Pharmacovigilance Initiative Research Coordinator at 604-806-8663 (weekdays).

For more information regarding adverse reaction reporting and HIV medication safety, refer to the BC-CfE website: http://bccfe.ca/hiv-drug-safety

APPENDIX: Technical information

Analytical methods used in the preparation of this report are summarized below:

Unless otherwise specified, the inclusion and exclusion criteria for all Adverse Drug Reaction (ADR) analyses are as follows:
Include: Events categorized as ADR (including ADRs resulting from drug interactions), see Definitions.
Exclude: Duplicate reports of the same event, ADRs with a causality assessment of "unlikely" to be associated with ARV(s), and reports of therapy change to prevent ADRs or drug interactions.
ADR rates are reported without consideration for the duration of drug therapy prior to the ADR report, or the duration of symptoms prior to the ADR report date.

Figure 1: Calculation of overall ADR rates for HIV-treatment and PrEP patients. Within each quarter (3-month period), the numerator is the number of ADR reports for ART-treated persons. The denominator is the total number of patient-years of ART exposure accrued during the quarter. The resulting ADR rate is multiplied by 100 to give events per 100 person-years of treatment. Error bars around each point display the 95% confidence interval, calculated by the Poisson method.

Figure 2-5: **Calculation of ADR rates, by antiretroviral drug.** Within each calendar year, the numerator is the number of ADR reports specifying an adverse reaction attributed to the drug of interest. The denominator is the total number of patient years exposure to the drug, accrued during the time period. The resulting ADR rate is multiplied by 100 to give events per 100 person-years of treatment. Error bars around each point display the 95% confidence interval calculated by the Poisson method.

Figures 6a-b: **Calculation of ADR Rates by symptom category**. ADR reports contribute data for each relevant clinical category once per person in the calendar year the ADR was reported.

ADR rates are calculated as follows: In each calendar year, the numerator is the number of ADR reports specifying an adverse reaction for the symptom class of interest. The denominator is the total number of patient-years exposure to antiretroviral therapy for treatment of HIV during the calendar year. The resulting RATE is multiplied by 100 to give events per 100 person-years of treatment. Error bars around each point display the 95% confidence interval calculated by the Poisson method.

Adverse drug reactions associated with ART for HIV treatment in special populations
Statistical comparisons between groups are calculated using Pearson's Chi-squared test.